REMARKS/ARGUMENTS

Claims 44-46 and 49-52 are pending in this application.

The present rejections to the claims are respectfully traversed.

Amendments

Applicants have canceled Claims 39-43 without prejudice to filing a continuation application directed to the canceled subject matter.

Applicants have amended Claim 44 to delete the recitation "wherein said polypeptide is overexpressed in lung tumor."

Applicants have amended Claim 50 to correct claim dependencies.

Applicants have added new Claim 52. Support for this claim can be found in original Claim 47 which was canceled.

No new matter is added by these amendments.

Drawings

Applicants are grateful for the decision that the formal drawing have been found acceptable by the Draftsman.

Priority

The Examiner acknowledges that Applicants have claimed priority to International Application PCT/US00/03565, filed February 11, 2000. However, the Examiner argues that the instant subject matter lacks the necessary support for priority under 35 U.S.C. §112 because the claims do not have specific and substantial utility.

As will be apparent from the discussions below and the Declaration by Dr. Avi Ashkenazi filed under 37 C.F.R. §1.132, Applicants submit that the results of the gene amplification assay (Example 92) provide specific and substantial asserted utility for the polypeptide PRO269. These results (Example 92) were first disclosed in PCT/US00/03565. Accordingly, the effective filing date of this application is February 11, 2000 and the claims pending are fully entitled to the priority of February 11, 2000.

IDS

Applicants' Supplemental IDS filed 2/21/03, was acknowledged, however the Examiner indicated that Genbank CNSLT115k (IDS #11) and GenBank CNSO7EEV (IDS #12) were not found and therefore have not been considered.

Applicants note that these references were in the papers submitted with the IDS. However, in order to expedite prosecution, Applicants again submit these references for consideration by the Examiner.

35 U.S.C. §101 Utility Rejection

Claims 39-46 and 49-51 stand rejected under 35 U.S.C. §101 because the claimed invention is allegedly not supported by either a credible, specific and substantial asserted utility or a well established utility.

A Declaration under 37 C.F.R. §1.132 by Dr. Goddard was previously filed supporting that the TaqMan™ PCR technique is technically sensitive enough to detect at least a 2-fold increase in gene copy number relative to control. Dr. Goddard concludes that a gene identified as being amplified at least 2-fold by the quantitative TaqMan™ PCR assay in a tumor sample is useful as a marker for the diagnosis of cancer, for monitoring cancer development and/or measuring the efficacy of cancer therapy.

The Examiner has noted that a second unexecuted Declaration by Dr. Goddard was also filed on 3/31/03. The Examiner notes that while similar arguments were advanced, 4-fold, rather than 2-fold amplification of a gene was described as significant. In response, Applicants note that the executed Declaration indicates that 2-fold amplification is significant. Clearly if 2-fold amplification is significant, then 4-fold amplification would also be significant. Accordingly, Applicants do not perceive a conflict between these documents. Applicants request that the Examiner rely on the executed Goddard Declaration.

The Examiner acknowledges that the results in Table 9 do show that the PRO269 gene had a ΔCt value of above 1 in 8 primary lung tumors. However, the Examiner indicates that the totality of the evidence allegedly does not support

Applicants' assertion that PRO269 is a diagnostic marker for lung cancer, because the ΔCt values are only slightly above 1 (which the Examiner states identifies the background of normal DNA), there is an absence of any signal in 9 other primary lung tumors, and there is an absence of controls for the aneuploidy of the samples. For the following reasons, Applicants respectfully disagree.

Evidentiary Standard

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re* Langer, 503 F.2d 1380,1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re* Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re* Irons, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. §101 is a question of fact. Raytheon v. Roper, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992) Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

According to the Utility Examination Guidelines, 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 USC 101 if it has at least one asserted "specific, substantial and credible utility". In explaining the "substantial utility", standard MPEP 2107.01 cautions that Office personnel must be careful not to interpret the phrase 'immediate benefit to the public" to mean that products or services based on the claimed invention must be "currently available" to the public. Rather, any

reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient at least with regard to defining a "substantial utility". Indeed, the Guidelines for Examination of Applications for Compliance with the Utility Requirement, set forth in MPEP 2107II(B) gives the following instruction to patent examiners: "If the Applicant has asserted that the claimed invention is useful for any particular practical purpose...and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility".

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible". Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record...that is probative of the applicant's assertions." (MPEP 2107 II (B)(1)(ii)) Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

Proper Application of the Legal Standard

Applicants submit that the gene amplification data provided in the present application as explained below and in the Goddard Declaration and the enclosed Ashkenazi Declaration is sufficient to establish a specific, substantial and credible utility for the PRO269 polypeptide to which the claimed antibodies are directed.

The Declaration by Audrey Goddard clearly establishes that the TaqMan™ realtime PCR method described in Example 92 has gained wide recognition for its versatility, sensitivity and accuracy and is in extensive use for the study of gene amplification. The Declaration confirms that based on the gene amplification results set forth in Table 9 one of ordinary skill would find it credible that PRO 269 is a diagnostic marker of human lung cancer.

The Examiner states that "from the discussion on page 22 of the disclosure (*e.g.*, lines 11-32) that a CT value of +/- 1 identifies background of normal human DNA

compared to test DNA." Applicants cannot find the quote that the Examiner is referencing. Applicants would direct the Examiner to pages 222, line 44 to page 223, line 223 which states "The results of the TaqMan™ are reported in delta (Δ) CT units. One unit corresponds to 1 PCR cycle or approximately a 2-fold amplification relative to normal, two units corresponds to 4-fold..." The Examiner acknowledges that the results in Table 9 do show that the PRO 269 gene had a ΔCT value above 1 in 8 primary tumor lines. The Declaration of Dr. Goddard confirms that an at least 2-fold increase in gene copy number in a tumor tissue sample relative to a normal (*i.e.,* non-tumor) is significant and useful.

It is well known that gene amplification occurs in most solid tumors and generally is associated with poor prognosis. As shown in Example 92 and Table 9, PRO269 showed approximately 2-3 fold amplification in 8 primary tumors. The Goddard Declaration previously submitted confirms that based upon the gene amplification results set forth in Table 9 one of ordinary skill would find it credible that PRO269 is a diagnostic marker of human lung cancer. Accordingly, PRO269 polypeptides would be useful to generate antibodies as diagnostic reagents for diagnosing lung tumors.

The Examiner indicates that because the gene is not amplified in 9 cell lines it cannot act as a diagnostic. Applicant disagrees. The gene is amplified in some cells lines. Accordingly, it clearly can act as a diagnostic for those lung tumors.

The Examiner indicates that because there were not controls for the aneuploidy of the samples, the totality of the evidence does not support utility. Enclosed is a Declaration by Avi Ashkenazi, Ph.D., an expert in the field of cancer biology. In his Declaration, Dr. Ashkenazi confirms that even in the absence of over-expression of the gene product, amplification of a cancer marker gene - as detected, for example by the reverse transcriptase TaqMan™PCR or the fluorescence *in situ* hybridization (FISH) assays - is useful in the diagnosis or classification of cancer, or in predicting or monitoring the efficacy of cancer therapy.

He states:

> "An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes"

Accordingly, aneuploidy does not need to be controlled for and clearly the results are significant.

35 U.S.C. §112, First Paragraph, Rejections

Claims 39-46 and 49-51 stand rejected under 35 USC §112, first paragraph, for alleged lack of enablement because the claimed invention is not supported by a credible, specific and substantial asserted utility, hence one skilled in the art clearly would not know how to use the claimed invention.

In response to the previous rejection under 35 U.S.C. §101, Applicants have shown that the specification discloses a substantial, specific and credible utility for the PRO269 polypeptide or antibodies against it. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection of all pending claims.

In explaining the rejection under 35 U.S.C. §112, first paragraph, the Examiner asserts on page 5, part A, that the claims are drawn to a polypeptide rather than a gene and even were a diagnostic utility established for the gene, it is unclear whether a specific and substantial utility for the polypeptide would follow, particularly in the absence of data supporting over-expression of the protein product that could be detected by an antibody reagent.

Applicants respectfully disagree.

The Examiner has not provided evidence that there is a lack or correlation between the gene amplification and over expression of the protein. Indeed, the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level.

Even if one assumes arguendo that it is more likely than not that there is no correlation between gene amplification and increased mRNA/protein expression, a polypeptide encoded by a gene that is amplified in cancer would still have a specific and substantial utility.

As Dr Ashkenazi explains in his Declaration:

> even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Accordingly, the PRO269 polypeptide and antibodies binding to it have a substantial specific utility. For the reasons set forth above, the present rejections under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph, for lack of utility should be withdrawn.

Claims 39-43 and 50-51 stand rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly does not reasonably provide enablement for polypeptides having less than 100% identity to at least the extracellular domain of SEQ ID NO:96.

In order to expedite prosecution, Applicants have canceled Claims 39-43 without prejudice to filing a continuation application directed to the canceled subject matter. Withdrawal of this rejection is respectfully requested.

Claims Rejection - 35 U.S.C. §112, First Paragraph, Written Description

Claims 39-43 and 50-51 also stand rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in

such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention.

In order to expedite prosecution, Applicants have canceled Claims 39-43 without prejudice to filing a continuation application directed to the canceled subject matter. Withdrawal of this rejection is respectfully requested.

Claim Rejections - 35 USC § 102(a)

Claims 39-46 and 49-51 stand rejected under 35 U.S.C. §102(b) or in the alternative under 35 U.S.C. §102(a) as being anticipated by Wood et al. (WO 99/14328). This rejection is traversed for the following reasons.

As discussed above, the claims pending in this application are entitled to the effective filing date of September 11, 2000. Wood et al., was published less than one year prior to the effective filing date of the present application. Accordingly, Wood et al. is not a 35 U.S.C. §102(b) prior art reference.

It is well established that Applicants' disclosure of their own work within the year before the filing date of a patent application cannot be used against Applicants under 35 U.S.C. §102(a) In re Katz, 687 F.2d 450, 215 USPQ 14 (1982). In the present case, the inventors of the present invention, namely, William Wood, Audrey Goddard, and Austin Gurney are co-inventors of the cited publication, Wood et al. Applicants submit herewith Declarations from each of William Wood, Audrey Goddard and Austin Gurney that the disclosure set forth in Wood et al. relating to PRO269 describes their own work to which the other listed inventors made no inventive contribution. This Declaration is believed to remove Wood et al. as a reference. Accordingly, the withdrawal of the present rejection is requested.

Claim 39-43 stand rejected under 35 U.S.C. §102(a) as being anticipated by Valenzuela et al. (WO 00/11015) (published March 2, 2000) which allegedly teaches a protein that is at least 100% identical to SEQ ID NO: 96.

As discussed above, the claims pending in this application are entitled to the effective filing date of September 11, 2000. The cited primary reference Valenzuela et al. has a publication date of 3/2/2000 which is after the effective filing date (9/11/2000)

of the present application. Hence, Valenzuela is not prior art under 102(b), and does not anticipate the present claims. Withdrawal of the rejection is respectfully requested.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (Attorney's Docket No. **39780-1618 P2C33**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: October 17, 2003

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